Lanreotide autogel and insulin sensitivity markers: Report of 5 acromegalic patients and literature review

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Abstract

OBJECTIVE: To evaluate the short-term effects of Lanreotide Autogel on insulin sensitivity markers among acromegalic patients with pituitary tumors.
DESIGN: Prospective clinical trial with six months of follow-up.
SETTING: A tertiary endocrinology clinic.
MATERIALS AND METHODS: Naïve patients (patient No. 1 and patient No. 3) and patients who experienced prior somatostatin analogue treatment (patient No. 2, patient No. 4, and patient No. 5) were included. Before and after 6 months of Lanreotide Autogel therapy, insulin sensitivity in each subject was determined using homeostasis model assessment of insulin resistance and beta-cell function formula. Euglycemic hyperinsulinemic clamp test was also performed to evaluate whole insulin sensitivity and was indicated as an 'M' index.
RESULTS: All patients experienced reduction in their HOMA-β. We noted major HOMA-β decreases accompanied by pronounced increases in M indices for patients Nos. 1, 2 and 3 (1.03 vs. 8.22, 2.98 vs. 4.70, and 5.09 vs. 13.09, respectively). The increases in M indices of these patients were with marked decreases in GH levels (34.20 vs. 15.30 µg/l, 4.25 vs. 0.74 and 5.0 vs. 0.66 ng/mL, respectively). Minor decline in HOMA-β and worsened M index and almost stable GH were observed in patients Nos. 4 and 5. Except for patient No. 3, all participants showed declining HOMA-IR.
CONCLUSIONS: Short-term Lanreotide Autogel treatment has been observed to improve M indices of acromegalic patients whose GH levels exhibited marked reduction. This amelioration seemed to be related to decreases in GH levels rather than to a direct drug effect.

CASE REPORT

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Abbreviations

GH	- Growth hormone
LA	- Lanreotide Autogel
IGF-1	- Insulin-like growth factor-1
O-LAR	- octreotide long-acting release
L-SR	- lanreotide slow release
SA	- somatostatin analogue
HOMA-IR	- homeostasis model assessment of insulin resistance
HOMA-β	- homeostasis model assessment of beta-cell function

INTRODUCTION

Disorders of glucose metabolism are severe complications frequently affecting acromegalic patients. Pancreatic β-cell dysfunction and insulin resistance have been claimed to be responsible for the pathogenesis (Hansen *et al.*, 1986; Jap & Ho, 1990; Foss *et al.*, 1991). Somatostatin analogues are a cornerstone of medical therapy for acromegaly. Naive somatostatin-14, inhibits the secretion of insulin and glucagon and several other peptide hormones besides suppressing GH (Alberti *et al.*, 1973; Koerker *et al.*, 1974). Insulin-mediated suppression of hepatic glucose production is strongly dependent on GH concentrations (Ho *et al.*, 1992).

Lanreotide is an octapeptide analogue of somatostatin that acts as a potent agonist against type 2 and type 5 somatostatin receptors expressed by GH-secreting tumors (Lightman, 2002). A prolonged release, supersaturated and aqueous formulation of lanreotide; Lanreotide Autogel (LA), administered every 28 days by deep subcutaneous injection from a prefilled syringe, has been developed to overcome the necessity of frequent injections. This form has been shown to lower plasma GH and insulin-like growth factor-1 (IGF-1) levels significantly leading to a considerable improvement in the complications of acromegaly (Caron *et al.*, 2002; Caron *et al.*, 2004; Gutt *et al.*, 2005; Tolis G *et al.*, 2006).

There are several studies which have shown the beneficial effects of octreotide long-acting release (O-LAR) and lanreotide slow release (L-SR) on insulin sensitivity among acromegalic cases. In those studies, insulin sensitivity was determined by using the simple computer-solved markers depending on fasting glucose and insulin levels (Ronchi *et al.*, 2002; Ronchi *et al.*, 2003), and the euglycemic hyperinsulinemic clamp method (Baldelli *et al.*, 2003; Sato *et al.*, 1995). However, there is limited number of reports with LA performed via using computer-solved markers only (Steffin *et al.*, 2006; Ronchi *et al.*, 2006).

Lack of solid evidence regarding the influence of LA on insulin sensitivity markers in literature prompted us to evaluate the short-term effects of this depot somatostatin analogue (SA) via using the euglycemic hyperinsulinemic clamp method and simple computer-solved markers among acromegalic patients.

MATERIALS AND METHODS

This prospective study had a follow-up of 6 months. Participants were acromegalic patients recruited from our outpatient endocrinology clinic. The Baskent University Ethics Committee for Human Studies approved the protocol. All patients provided written informed consent. Newly diagnosed patients and those patients who had failure with octreotide treatment and the ones who approved to switch to LA every 28 days were included at the Endocrinology Clinic of Baskent University Faculty of Medicine in Adana, Turkey.

Duration of the disease was estimated according to acromegalic signs and symptoms based on patient-self-reports, medical records, and family photographs. Activity of the disease was confirmed by elevated age- and sex-corrected plasma IGF-1 levels, high baseline plasma GH levels (>2.5 ng/ml), and nonsuppressible GH (>1 ng/ml) after an oral glucose tolerance test (Giustina *et al.*, 2000).

Patients and Study protocol (T: time point)

Baseline GH and IGF-1 measurements plus oral glucose tolerance test with 75 g glucose for GH suppression and determination of insulin sensitivity markers were performed in each patient at inclusion, (n=5), (T1).

On the next day following the procedures mentioned above, the cases were subjected to euglycemic hyperinsulinemic clamp test, (T2).

Fifteen days after the third injection, basal GH and IGF-1 measurements were repeated in patients Nos. 1, 3 and 5, (T3).

Growth hormone, IGF-1, fasting blood glucose and insulin measurements plus re-performance of euglycemic hyperinsulinemic clamp test were held fifteen days after the 6th injection, (n=5), (T4).

Pituitary magnetic resonance imaging procedures were done both at the beginning and at the end of the study period.

Patient No. 1 was a 40-year-old naive acromegalic man detected to have a pituitary macroadenoma, 16x8mm in size. It was not possible to estimate the duration of his disease, as he could neither define the time of onset of the disease-related symptoms nor could he present a personal photograph taken in earlier periods. There was no indication for urgent surgery, so LA (90mg) was planned to be given as first-line treatment. Biochemical re-evaluation was performed after the third injection of LA and the dose was increased up to 120mg. At the end of follow-up, tumor was found to shrink significantly with a size of 8x4mm. Final IGF-1 level was normalized and GH decreased to half of its original level.

Patient No. 2 was a 26-year-old acromegalic woman who had experienced unsuccessful pituitary surgery for twice and a session of conventional radiotherapy (5 400 cGy in total) for a macroadenoma that exhibited

bulky residual tumor mass (37×26 mm in size at diagnosis). She had inadequate biochemical response despite 36 months of therapy with O-LAR 40 mg (two 20 mg O-LAR syringes) every 28 days and cabergoline 1mg per week. She reported to have acromegalic signs and symptoms for at least 7 years. The tumor was shown to invade the surrounding structures and no definite tumor size could be mentioned at inclusion. Octreotide treatment was switched to LA 120 mg every 28 days. Her final pituitary imaging exhibited no reduction in residual tumor mass, despite of a satisfactory biochemical response in terms of GH and IGF-1.

Patient No. 3 was a 46-year-old-woman who had been taking cabergoline (1.5 mg per week) for the giant lacto-somatotroph adenoma (60×50 mm in size; diagnosed by biochemical evaluation) for the last 8 months. She had had the history of cessation of menstrual periods for 13 years which enabled our estimation of duration of the disease. Baseline severe prolactin elevation with macroprolactin absence (serum prolactin >40 000 mIU/L, normal ranges: 33.36–580.80) returned to normal levels during cabergoline treatment, and the adenoma was shown to regress about the half of its original size and stabilized at this volume without further regression. Sustained elevation in IGF-1 and non-suppressible GH levels following an oral glucose load, convinced us to add LA (90 mg) to the regimen. The dose of LA remained the same all through the study period, as the evaluation performed on the third month revealed biochemical regression. At final investigation, her IGF-1 was found to remain elevated, despite of a satisfactory decrease in basal GH level. Her pituitary MRI exhibited insignificant reduction in tumor size.

Patient No. 4 was a 40-year-old acromegalic man with a history of unsuccessful pituitary surgery due to a macroadenoma with an original size of 13×10 mm. He had had two 20 mg O-LAR syringes injected every 28 days for 17 months prior to switching treatment to LA (120 mg), owing to his persistent requests to be treated with only 1 injection at a time. The duration of his disease was approximately 6 years. The residual tumor was 8×4 mm in size. Tumor size remained the same following six months of LA treatment and he exhibited suppressed basal GH and high IGF-1 levels.

Patient No. 5 was a 35-year-old acromegalic man who was operated for a pituitary adenoma that compressed the optic tract. He had the history of gamma-knife radiosurgery (46 Gy maximally) performed 4 months after the operation. He had been taking octreotide short-acting form 300 μg/day for a year and had a 2 cm residue adenoma in size when he admitted to our outpatient clinic. The acromegalic signs and symptoms of the patient pointed more than two years in duration of disease. Short-acting octreotide was withdrawn a month before performing the study procedures. Lanreotide Autogel 90mg every 28 days was planned to be given. Considering the decrease

in basal GH and IGF-1 levels detected at T3, the dosage remained the same all through the study period. His final biochemical investigation revealed active disease and there was no reduction in tumor size.

Venous blood samples were withdrawn for glucose and insulin measurements following a 12-hour overnight fasting both at T1 and T4. Patients Nos. 1, 3 and 5 were prescribed a long-acting SA for the first time at an average estimated dose, so might need further dose adjustment. GH and IGF-1 measurements were re-performed fifteen days after the third injection (T3) in these cases for dose adjustment. Patients Nos. 2 and 4 had already been taking high doses of O-LAR when their treatments were switched to maximum available doses of LA, therefore no further dose adjustment was planned. Depending on a previous report, no wash-out period was given and first LA injections were performed a few days after the supposed depot octreotide injection time (Cozzi *et al.*, 1999).

Patient No. 2 was prescribed cabergoline due to the favorable effects of the combination therapy; cabergoline plus depot SA, in the control of resistant acromegalic patients (Cozzi *et al.*, 2004). As the latter subject and patient No. 3 had been taking the drug for months, a decision was made in favor of not withdrawing cabergoline throughout the study period.

Characteristics of the patients are shown in Table 1.

Euglycemic hyperinsulinemic clamp method defined by DeFronzo was used, and insulin sensitivity was derived from glucose disposal rate expressed as mg/kg/min and indicated as 'M' index (DeFronzo *et al.*, 1979). Insulin resistance and beta-cell function were calculated by using the homeostasis model assessment of insulin resistance (HOMA-IR) and beta-cell function (HOMA-β) formulas [fasting plasma insulin (mU/l) x fasting plasma glucose (mmol/l)/22.5] for HOMA-IR and [fasting plasma insulin (mU/l)×20 / fasting plasma glucose (mmol/l) – 3.5] for HOMA-β (Matthews *et al.*, 1985).

We considered successful control of acromegaly to occur when GH levels were suppressed below 2.5 ng/ml in fasting samples and when IGF-1 levels were normalized for age- and sex-adjusted limits (Giustina *et al.*, 2000).

Laboratory Analyses

Serum glucose was measured by the glucose oxidase technique (Roche Diagnostics GmbH, Mannheim, Germany). Insulin levels were measured using the AxSYM Immunoassay system with micro-particle enzyme immunoassay (MEIA) (Abbott Laboratories, Abbott Park, IL, USA) with an average interassay coefficient of variation of 5.3% and intraassay coefficient of variation of 4.1%. GH levels were calculated using solid-phase, competitive chemiluminescent enzyme immunoassays on an Immulite analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA). Inter- and intraassay coefficients of variation were less than 8.5%. The IGF-1 measurements of patients Nos. 3, 4 and 5 were also

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Table 1. General features of the patients regarding history of the disease and follow-up outcomes (n=5).

Patient #	Age (y)/sex	d.d. (y)	Adenoma size at diagnosis (mm)	Previous treatment	Duration and content of medical therapy at inclusion	LA dosage initial/final (mg)	Adenoma size at inclusion/final
Patient No. 1	40/M	?	16	–	–	90/120	16 mm/8 mm
Patient No. 2	26/F	7	37	-PS (2 times) -cRT (5 400 cGy in total)	36 months -Octreotide LAR 40 mg × 28 days -Cabergoline 1 mg/wk	120/120	Giant adenoma with indefinite borders/ no reduction
Patient No. 3	46/F	13	60	-MT	8 months -Cabergoline 1.5 mg/wk	90/90	About half of its original size/ no reduction
Patient No. 4	40/M	6	13	-PS	17 months -Octreotide LAR 40 mg × 28 days –	120/120	8 mm/ no reduction
Patient No. 5	35/M	2	30	-PS -Gamma-knife radiosurgery (46 Gy maximally)	12 months -300 µg/day octreotide short-acting	90/90	20 mm/ no reduction

Abbreviations: M: male, F: female, d.d.: duration of disease, PS: pituitary surgery, cRT: conventional radiotherapy, MT: medical treatment, Ocreotide-LAR: Ocreotide long-acting release, LA: Lanreotide Autogel

Table 2. Patient characteristics regarding disease activity markers at T1 & T4 (T: time point).

Patient # T: Time point	Patient No. 1	Patient No. 2	Patient No. 3	Patient No. 4	Patient No. 5
Basal GH (T1) (µg/l) (0.00–5.00)	34.20	4.25	5.0	1.2	5.8
Basal IGF-1 (T1) (ng/ml)	886.0 (140–405)	209 (109–731)	485 (94–210)	310 (94–210)	1462 (109–293)
GH (following OGTT at 120th minute) (T1) (µg/l) (0.0–5.0)	24.80	3.0	1.20	0.87	3.4
Basal GH (T4) (µg/l) (0.0–5.0)	15.30	0.74	0.66	1.00	3.20
IGF-1 (T4) (ng/ml)	214 (54–336)	187 (116–358)	405 (94–210)	352 (94–210)	650 (109–293)

OGTT: Oral Glucose Tolerance Test
*Values in parenthesis under IGF-1 levels are the normal sex- and age-adjusted limits for each patient. The differences in IGF-1 normal ranges in patients Nos. 1 and 2 between periods T1 and T4 result from the performance of these measurements at laboratories other than ours.

performed with the analyzer mentioned above. However, the measurements of patients Nos. 1 and 2 at periods T1 and T4 were carried out at the laboratories other than ours which happened out of our control. This inevitably resulted in different laboratory ranges.

RESULTS

The GH and IGF-1 levels at T1 & T4 are given in details in Table 2 and GH change in each participant is graphically shown in Figure 1.

Baseline and final body weight, blood glucose and insulin levels are also given in details in Table 3.

Initial and final HOMA-IR and HOMA-β (%) were; 2.32 vs. 2.25 and 95 vs. 58.48 for patient No. 1, 2.31 vs. 0.41 and 289.15 vs. 83.63 for patient No. 2, 4.29 vs. 5.59 and 152.25 vs. 98.06 for patient No. 3, 3,23 vs. 2.59 and 76.87 vs. 67.14 for patient No. 4, 4.36 vs. 3.45 and 228.91 vs. 218.05 for patient No. 5, (shown in Figure 2 and 3).

The M indices of the cases prior and after 6 months of LA therapy were; 1.03 vs. 8.22 for patient No. 1, 2.98 vs. 4.70 for patient No. 2, 5.09 vs. 13.09 for patient No. 3, 5.72 vs. 5.53 for patient No. 4, 3.90 vs. 3.35 for patient No. 5, (shown in Figure 4).
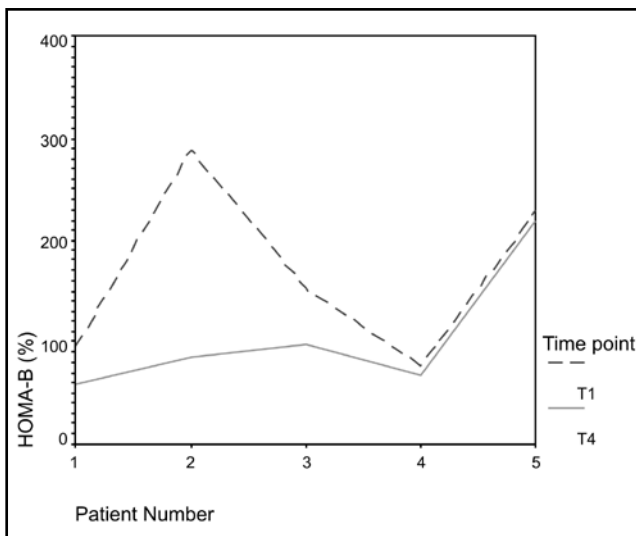
All patients experienced reduction in their HOMA-β values. Patients Nos. 1, 2, and 3 exhibited improvement
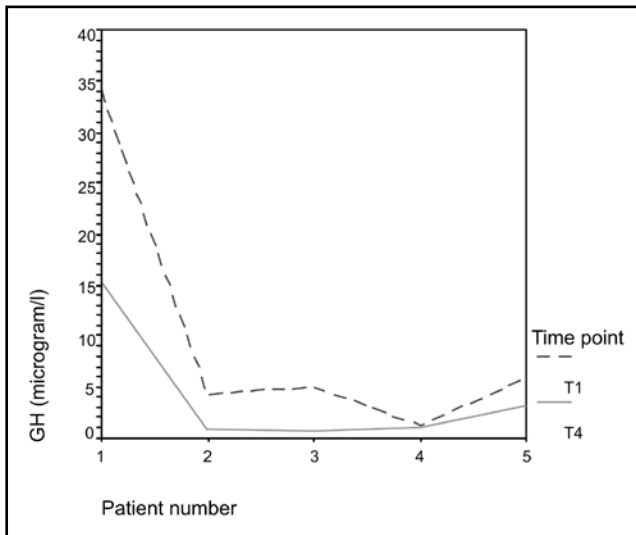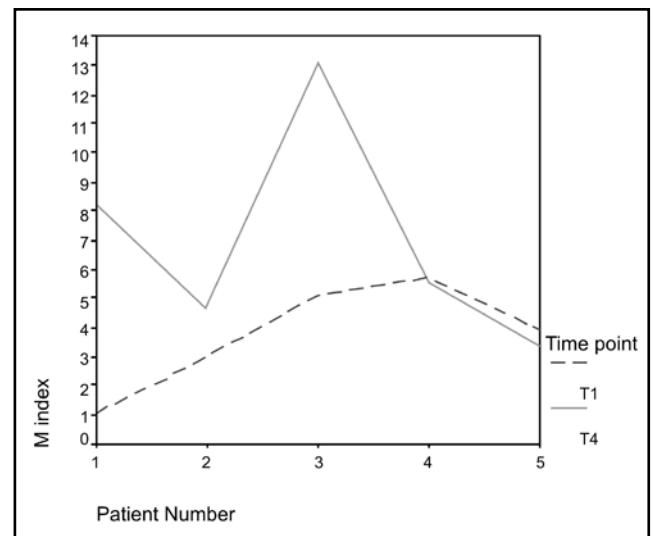
Figure 1. GH levels before and after treatment with Lanreotide Autogel (T1 & T4).
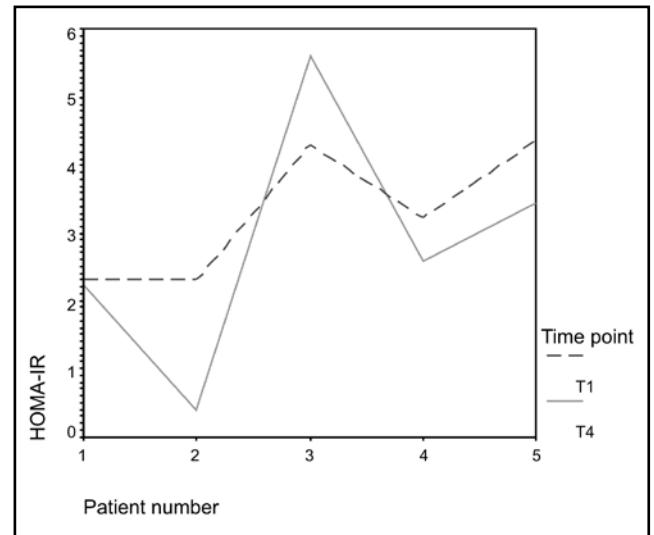
Figure 2. HOMA-IR values before and after treatment with Lanreotide Autogel (T1 & T4).

Figure 3. HOMA-B(%) before and after treatment with Lanreotide Autogel (T1 & T4).

Figure 4. M index before and after treatment with Lanreotide Autogel (T1 & T4).

in their M indexes accompanied by marked GH reductions. Except for patient No. 3, all participants showed declining HOMA-IR levels.

Three patients (60%) (patients Nos. 2, 3 and 4) reached desired final GH levels, whereas 2 patients (40%) (patients Nos. 1 and 2) achieved suggested IGF-1 levels. Only patient No. 1 (20%) exhibited a reduction in tumor size.

DISCUSSION

Acromegaly is an uncommon disease with an annual incidence about 3–4 cases per billion. Better diagnostic opportunities in recent years are accompanied by better outcome of surgical and pharmacological treatment and better control of the complications of the disease (Bolanowski *et al*., 2006). To the best of our knowledge, this

is the first study to examine the impact of LA on insulin sensitivity markers using the gold standard method: the euglycemic hyperinsulinemic clamp, in addition to HOMA-IR and HOMA-β calculations. One recent study reported that acromegalic patients treated with LA had indifferent HOMA-IR and significantly lower HOMA-β levels when compared with their untreated pairs (Steffin *et al*., 2006). The authors concluded that LA decreased β-cell function significantly without affecting HOMA-IR. In the present study, we also observed decline in all HOMA-β values; an effect which might be attributed to the inhibition of pancreatic insulin secretion by the somatostatin analogue. However, the effect of LA on HOMA-IR was obscure. Among non-diabetic cases (patients Nos. 1, 2, 4 and 5), the HOMA-IR values tended to decrease with LA therapy. Similar findings were reported in a few previous studies with the lanreotide slow release

Table 3. Characteristics of the participants at baseline vs following 6 months of treatment.

Patient #	Patient No. 1	Patient No. 2	Patient No. 3	Patient No. 4	Patient No. 5
Weight (kg)	76.6 vs. 74.5	59.7 vs. 58.7	86.4 vs. 85.7	88.10 vs. 85.9	106.3 vs. 105.9
Plasma glucose (mmol/l)	5.49 vs. 6.27	4.32 vs. 4.05	5.71 vs. 7.10	6.43 vs. 6.27	5.16 vs. 4.93
Plasma insulin (pmol/l)	65.97 vs. 56.25	83.34 vs. 15.97	117.37 vs. 122.92	78.47 vs. 64.58	131.95 vs. 109.03

form (Ronchi *et al.*, 2002; Ronchi *et al.*, 2003). Only in the mildly diabetic case (patient No. 3), the HOMA-IR even worsened, despite of improved M index. This finding is most likely due to her underlying diabetic milieu. She was diagnosed to have diabetes following an oral glucose tolerance test. The HOMA-IR might not be a reliable tool to determine the glucose homeostasis of this acromegalic case with diabetes.

We noted pronounced HOMA-β decreases accompanied by marked increases in M indices for patients Nos. 1, 2 and 3. Moreover, these increases in M indices were in parallel with the decreases in patients' GH levels. Minor decline in HOMA-β and GH, and worsened M index were observed in patients Nos. 4 and 5. Short-term Lanreotide Autogel treatment seemed to improve whole insulin sensitivity in acromegalic patients who were responsive to medical treatment in means of GH control. In the light of the well-known negative effect of GH on insulin sensitivity, it seems likely that the improvement in whole insulin sensitivity seen in our patients was mediated by a reduction in GH rather than a direct drug effect. These findings strengthen the hypothesis that improvement in insulin sensitivity by somatostatin analogues takes place at insulin receptor site by lowering plasma GH and insulin levels (Baldelli *et al.*, 2003; Sato *et al.*, 1995).

In a recent study, O-LAR has been shown to be more detrimental to glucose metabolism than the L-SR (Ronchi *et al.*, 2002). In the present study, patients Nos. 1 and 3 were prescribed a long acting somatostatin analogue, in this case LA, for the first time, and both revealed marked improvement in their M indices. Although patient No.2 who had been on O-LAR for 36 months before the study, exhibited amelioration in M index, it was not as prominent as in the cases mentioned above. Conflicting with these cases, patients Nos. 4 and 5 had worsened M indices. It seems not possible to make a comment regarding the net effect of LA on glucose metabolism depending on these findings.

It is known that dopamine agonists have positive effects on insulin sensitivity (Serri *et al.*, 2006). We had two acromegalic patients receiving fixed dosages of cabergoline with normal prolactin levels long before the study was begun and all the tests regarding insulin dynamics were carried without changing the doses. Hence, the re-

sults of our study dealing with the effect of LA on insulin sensitivity is thought to be unaffected by the dopamine agonist regimen of those specific cases.

Considering the previous reports about acromegaly, our work is the first prospective study analyzing the LA effects on insulin dynamics with the clamp technique, in fact carried with small number of cases. Infrequency of acromegaly in general population and the difficulties in performing the clamp test twice for each individual inevitably resulted in a limited number of patients included as it is in literature where clamp studies have been carried out on a small number of cases so far. We are aware of the fact that our results may not be statistically significant, however, we believe they are worth being discussed on individual basis. Further studies with large numbers of acromegalic participants should be performed to find out a clear cut effect of LA on insulin dynamics. For such a powerful study, all the cases should undergo an euglycemic hyperinsulinemic clamp test both before and after the drug has been started.

In conclusion, we observed that short-term Lanreotide Autogel treatment improved whole insulin sensitivity indicated as M index in acromegalic patients whose GH levels exhibited reduction. This amelioration seemed to be related to decreases in GH levels rather than to a direct drug effect.

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